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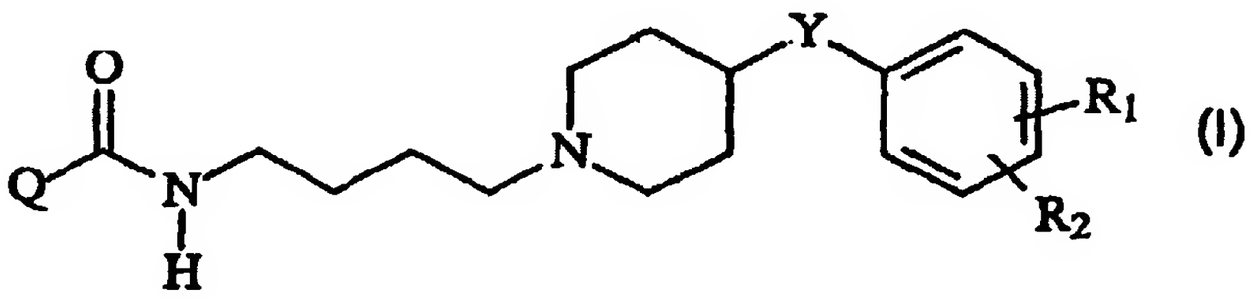
(54) Title: 4-(1-PIPERIDINY)-BUTYLCARBOXAMIDE AS D3 DOPAMINE RECEPTOR SUBTYPE SELECTIVE LIGANDS



(I)

(57) Abstract: The present invention relates to new D_3 dopamine receptor subtype selective ligands of Formula (I), wherein R_1 and R_2 represent independently a substituent selected from hydrogen, halogen, C_{1-6}alkyl, C¿1-6 ?alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6}alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6}alkanoyloxy, amino, aminoalkyl, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl or mono or bicyclic heterocyclic group; Y represents an oxygen atom or NH or CH_2 or OCH_2 group; Q represents an optionally substituted C_{1-6}alkyl, aryl, heteroaryl, heteroaralkyl or heteroaralkenyl group, and/or geometric isomers and/or stereoisomers and/or diastereomers and/or the salts and/or hydrates and/or solvates thereof, to the process for producing the same, to pharmacological compositions containing the same and to their use in therapy and/or prevention of psychoses (e.g. schizophrenia, schizo-affective disorders, etc.), drug (e.g. alcohol, cocaine and nicotine, opioids, etc.) abuse, cognitive impairment accompanying schizophrenia, mild-to-moderate cognitive deficits, amnesia, eating disorders (e.g. bulimia nervosa, etc.), attention deficit/hyperactivity disorder in children, psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders (e.g. Parkinson's disease, neuroleptic induced parkinsonism, tardive dyskinesias) anxiety, sexual disorders, sleep disorders, emesis, aggression, autism, pain, ophthalmological diseases (e.g. glaucoma, etc.).

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CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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4-(1-PIPERIDINYL)-BUTYLCARBOXAMIDE AS D3 DOPAMINE RECEPTOR SUBTYPE SELECTIVE LIGANDS

Field of the invention

The present invention relates to new D_3 dopamine receptor subtype selective ligands of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof, to the processes for producing the same, to pharmacological compositions containing the same and to their use in therapy and/or prevention of a condition which requires modulation of dopamine receptors.

Description of the prior art

Fused imidazo-pyridine derivatives are described in patent applications WO 9740051 and WO 9720632 having antihyperglycemic activity.

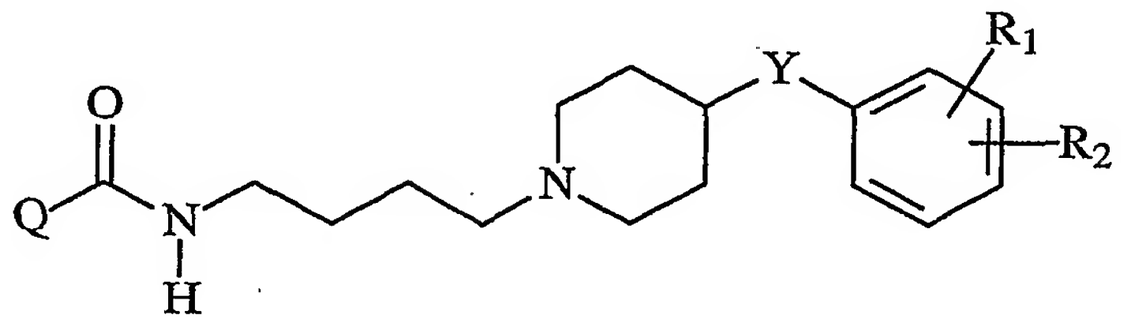
Dihydropyridine derivatives for the treatment of benign prostatic hyperplasia are disclosed in patent US 5 767 131.

The compounds mentioned in the above publications are not declared or even not suggested having activity on the dopamine D_3 receptors.

Summary of the invention

Surprisingly it was found that in contrast to the known above mentioned structurally analogous compounds the new derivatives of formula (I) of the present invention have high affinity for dopamine D_3 receptors and selectivity over other receptors, especially dopamine D_2. The selectivity is particularly important as the undesired side effect of the compounds are much less pronounced.

The invention relates to new piperidinyl compounds having carboxylic acid amide structures of formula (I):



(I)

wherein

R_1 and R_2 represent independently a substituent selected from hydrogen, halogen, C_{1-6}alkyl, C_{1-6} alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6} alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6} alkanoyloxy, amino, aminoalkyl, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl or mono or bicyclic heterocyclic group;

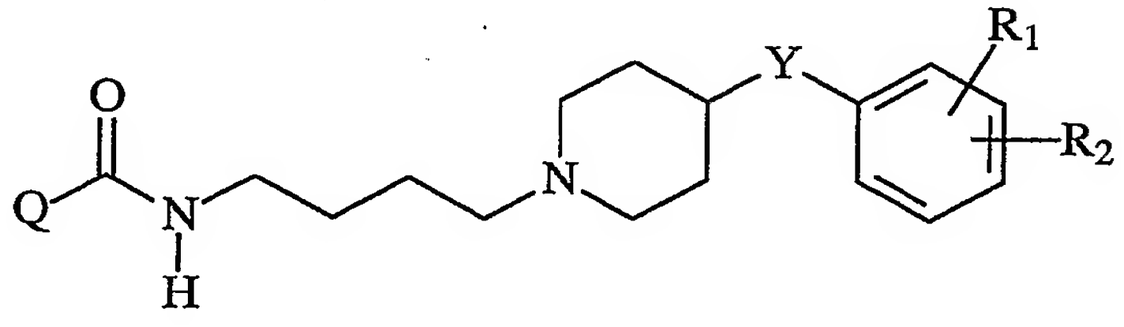
Y represents an oxygen atom or NH or CH_2 or OCH_2 group;

Q represents an optionally substituted C_{1-6}alkyl, aryl, heteroaryl, heteroaralkyl or heteroaralkenyl group,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof, to the processes for producing the same,to pharmacological compositions containing the same and to their use in therapy and/or prevention of psychoses (e.g. schizophrenia, schizo-affective disorders, etc.), drug (e.g. alcohol, cocaine and nicotine, opioids, etc.) abuse, cognitive impairment accompanying schizophrenia, mild-to-moderate cognitive deficits, amnesia, eating disorders (e.g. bulimia nervosa, etc.), attention deficit disorders, hyperactivity disorders in children, psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders (e.g. Parkinson's disease, neuroleptic induced parkinsonism, tardive dyskinesias) anxiety, sexual dysfunction, sleep disorders, emesis, aggression, autism, pain, ophthalmological diseases (e.g. glaucoma, etc.).

Detailed description of the invention

The invention relates to new piperidinyl compounds having carboxylic acid amide structures of formula (I):



(I)

wherein

R_1 and R_2 represent independently a substituent selected from hydrogen, halogen, C_{1-6}alkyl, C_{1-6} alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6} alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6} alkanoyloxy, amino, aminoalkyl, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl or mono or bicyclic heterocyclic group;

Y represents an oxygen atom or NH or CH_2 or OCH_2 group;

Q represents an optionally substituted C_{1-6}alkyl, aryl, heteroaryl, heteroaralkyl or heteroaralkenyl group,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

When Q represents aryl, the aryl moiety may be selected from an optionally substituted mono-, bi- or tricyclic aryl such as phenyl, naphthyl, fluorenonyl, or antraquinonyl group.

A heteroaryl ring in the meaning of Q may be monocyclic, bicyclic or tricyclic ring.

The monocyclic heteroaryl ring may be an optionally substituted 5- or 6-membered aromatic heterocyclic group containing 1 to 4 heteroatoms selected from O, N or S.

Examples of 5- and 6-membered heterocyclic groups include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl,

triazinyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl and pyrazolyl, preferably pyridyl and thienyl.

Examples of bicyclic heteroaromatic groups include indazolyl, indolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, quinoxolinyl, quinazolinyl, cinnolinyl, isoquinolinyl, preferably quinolinyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzimidazolyl and indolyl group.

Example of a tricyclic heteroaromatic group include beta-carboline.

The substituents of C_{1-6}alkyl, aryl, heteroaryl, heteroaralkyl or heteroaralkenyl group in the meaning of Q are selected from hydrogen, halogen, hydroxy, cyano, amino, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6} alkanoyl, methylenedioxy, C_{1-6}alkylamino, C_{1-6}alkanoylamino, optionally substituted aroyl, aryloxy, aminosulfonyl, arylsulfonylamido, optionally substituted mono or bicyclic aromatic or heteroaromatic ring, wherein the aryl has the same meaning as mentioned above.

The substituents of C_{1-6}alkanoyloxy in the meaning of R_1 and R_2 are selected from hydrogen or halogen.

The amino, aminoalkyl, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl and sulfamoyl groups in the meaning of R_1 and R_2 may optionally be substituted on the N atom.

The mono or bicyclic heterocyclic group in the meaning of R_1 and R_2 may be saturated or unsaturated containing 1 to 4 heteroatoms selected from O, N or S.

The substituents R_1 and R_2 may be the same or different.

In the compounds of formula (I) an alkyl group or moiety in alkoxy, alkanoyl, alkanoylamino, alkanoyloxy groups may be straight or branched included methyl, ethyl, n-propyl, n-butyl, n-pentyl- n-hexyl and branched isomers thereof such as isopropyl, t-butyl, sec-butyl, and the like.

The alkenyl moiety in the meaning of heteroalkenyl in Q may have 1 to 6 carbon atoms and 1 to 3 double bonds.

The halogen substituent(s) in the compounds of formula (I) may be fluorine, chlorine, bromine or iodine, preferably fluorine, bromine and chlorine.

The invention relates also to the salts of compounds of formula (I) formed with acids.

Both organic and inorganic acids can be used for the formation of acid addition salts. Suitable inorganic acids can be for example hydrochloric acid, sulfuric acid, nitric acid and phosphoric acid. Representatives of monovalent organic acids can be for example formic acid, acetic acid, propionic acid, and different butyric acids, valeric acids and capric acids. Representatives of bivalent organic acids can be for example oxalic acid, malonic acid, maleic acid, fumaric acid and succinic acid. Other organic acids can also be used, such as hydroxy acids for example citric acid, tartaric acid, or aromatic carboxylic acids for example benzoic acid or salicylic acid, as well as aliphatic and aromatic sulfonic acids for example methanesulfonic acid, naphtalenesulfonic acid and p-toluenesulfonic acid. Especially valuable group of the acid addition salts is in which the acid component itself is physiologically acceptable and does not have therapeutical effect in the applied dose or it does not have unfavourable influence on the effect of the active ingredient. These acid addition salts are pharmaceutically acceptable acid addition salts. The reason why acid addition salts, which do not belong to the pharmaceutically acceptable acid addition salts belong to the present invention is, that in given case they can be advantageous in the purification and isolation of the desired compounds.

Solvates and/or hydrates of compounds of formula (I) are also included within the scope of the invention.

Certain compounds of formula (I), when the compound contains C_{1-6} alkenyl group can exist in the form of *cis*- and/or *trans*- isomers. These are likewise within the scope of the present invention including all such isomers and the mixtures thereof.

Certain compounds of formula (I) can exist as stereoisomers and diastereomers. These and the mixtures thereof are likewise within the scope of the present invention.

As the invention relates also to the salts of compounds of formula (I) formed with acids, especially the salts formed with pharmaceutically acceptable acids, the

meaning of compound of formula (I) is either the free base or the salt even if it is not referred separately.

Preferred compounds of the invention are those compounds of formula (I), wherein

R_1 and R_2 represent independently halogen or trifluoromethyl, cyano, alkoxy, alkyl, hydroxy, alkansulfonyloxy, aminocarbonyl;

Q represents optionally substituted alkyl, phenyl, biphenylyl, naphthyl, pyridyl, indolyl, indolylethenyl, carbolinyl, benzothiophen-yl, benzofuranyl or quinolinyl;

Y represents an oxygen atom or NH or CH_2 or OCH_2 group;

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

Especially preferred compounds of the invention are those compounds of formula (I) wherein

R_1 and R_2 represent independently halogen or trifluoromethyl;

Q represents 4-methylphenyl, 4-bromophenyl, 4-chlorophenyl, 2-naphthyl, 4'-hydroxy-biphenylyl, indol-5-yl, indol-3-ethenyl, 4-(imidazo[2,1-b]thiazol-6-yl)phenyl, 4-(imidazo[1,2-a]pyridin-2-yl)phenyl, β-carbolin-3-yl, 5-methoxy-benzothiophene-2-yl, 6-methoxy-benzofuran-2-yl, 3-quinolinyl, 4-quinolinyl;

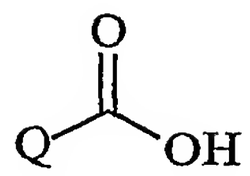
Y represents an oxygen atom or NH or CH_2 group;

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

The invention also relates to the pharmaceutical compositions containing the compounds of formula (I) as active ingredient.

Further subject of the present invention is the pharmaceutical manufacture of medicaments containing compounds of formula (I), as well as the process of treatments and/or prevention with these compounds, which means administering to a mammal to be treated - including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament.

The present invention also provides a process for preparing compounds of formula (I) by forming an amide bond between a carboxylic acid of formula (II):

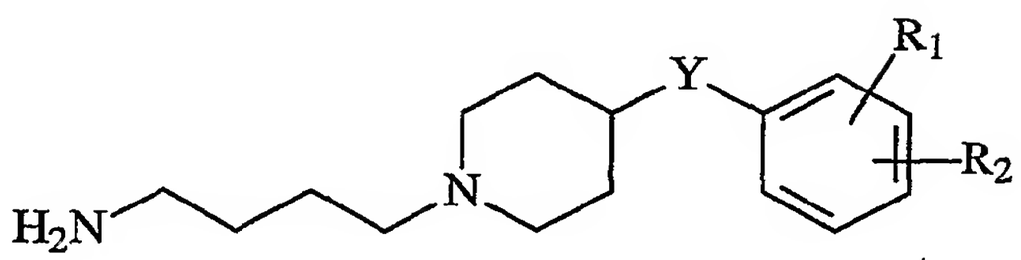


(II)

or derivatives thereof

wherein Q is as described above for the formula (I); and

an amine of formula (III):



(III)

wherein the meanings of R_1, R_2 and Y are as described above for the formula (I); or derivatives thereof.

The amide bond formation may be carried out by known methods, preferably by preparing an active derivative from a carboxylic acid of formula (II) and this active derivative is reacted with an amine of formula (III) in the presence of a base.

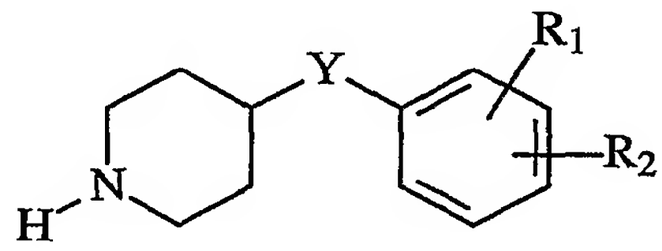
The transformation of a carboxylic acid into an active derivative may be carried out in situ during the amide bond formation in a suitable solvent (for example dimethylformamide, acetonitrile, tetrahydrofurane, chlorinated hydrocarbons or hydrocarbons). The active derivatives can be acid chlorides (prepared for example from carboxylic acid with thionyl chloride), mixed anhydrides (prepared for example from carboxylic acid with isobutyl chloroformate in the presence of a base, e.g. triethylamine), active esters (prepared for example from carboxylic acid with hydroxybenztriazole and dicyclohexyl-carbodiimide in the presence of a base, e.g. triethylamine). The active derivatives can be prepared advantageously between -10°C and room temperature. To the thus obtained solution or suspension an appropriate amine of formula (III) is added in a form of base or of salt formed with organic or inorganic acid. The condensation reactions are followed by thin layer chromatography. The necessary reaction time is about 6-20 h. The work-up of the reaction mixture can be carried out by different

methods. The products can be purified, e.g. by crystallization or by column chromatography.

The carboxylic acids of formula (II) are either commercially available or can be synthesized by different known methods (e.g. 6-methoxybenzofuran-2-carboxylic acid: J.Chem.Soc., **1940,** 787; 6-methoxybenzothiazole-2-carboxylic acid: J.Am.Chem.Soc., **1963,** 85, 337; 5-methoxybenzothiophene-2-carboxylic acid: J.Org.Chem., **1961,** 26, 1326; 4-imidazo[1,2-a]pyridin-2-yl-benzoic acid: WO 9534540; (4-pyrimidin-4-yl)-benzoic acid: WO 9957113; 9H-β-carboline-3-carboxylic acid: Heterocycles **1998,** 48, 993).

The syntheses of some commercially not available carboxylic acids of formula (II) are described in the Examples. Following these procedures the other commercially not available carboxylic acids of formula (II) can also be prepared.

The amines of formula (III) may be prepared by alkylation of compounds of formula (IV):



(IV)

wherein the meanings of R_1, R_2 and Y are as described above for formula (I);
or derivatives thereof

by standard methods.

Thus for example compound (IV) may be reacted with N-(4-bromobutyl)phthalimide followed by the removal of the phthaloyl group to give compound (III) or - where R_1 and R_2 are indifferent to reducing agents – by alkylation with 4-bromobutyronitrile followed by reduction of the cyano group.

The piperidines of formula (IV) may be prepared by known methods (e.g. where Y stands for NH group: Synlett, **1961,** 537; where Y stands for oxygen: J.Med.Chem., **1974,** 17, 1000; where Y stands for CH_2 group: US 3,632,767; WO 97/23216; FR 2,534,580).

The obtained carboxylic acid amide derivatives of formula (I) – independently from the method of preparation – can be transformed into an other

compound of formula (I) in given case by introducing further substituent(s) and/or modifying and/or removing the existing one(s).

For example cleaving the methyl group(s) from methoxy group(s) which stand for R^1 and/or R_2 leads to phenol derivatives. The cleavage of methyl group(s) can be carried out, e.g. with boron tribromide in dichloromethane solution. The compounds of formula (I) containing free phenolic hydroxy group(s) can be transformed into acyloxy or sulfonyloxy derivatives thereof with different acylating or sulfonylating agents. The reactions are carried out at room temperature in chlorinated hydrocarbons using acid chloride or acid anhydride as acylating agent in the presence of a base (for example triethylamine or sodium carbonate).

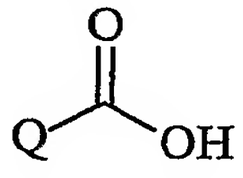
The compounds of formula (I) containing cyano group(s) e.g. can be transformed to amides by hydrolysing them with hydrogenperoxide in dimethylsulfoxide, or to amidines by reacting them first with gaseous hydrogenchloride in ether, then by reacting the iminoester obtained with ammonia, etc.

The obtained carboxylic acid amide derivatives of formula (I) can be transformed into the salts thereof with acids and/or liberated the carboxylic acid amide derivative of formula (I) from the obtained acid addition salts by treatment with a base, and/or can be separated the *cis*- and/or *trans*-isomers and/or the stereoisomers and/or diastereomers and/or can be transformed into hydrates and/or solvates thereof.

The carboxamide derivatives of formula (I) can also be prepared on solid support, e.g. in the following way.

A protected 4-aminobutanol derivative e.g. triisopropylsilanyloxy-butylamine is attached to a polystyrene resin e.g. 4-formyl-3-methoxy-phenoxy polystyrene by reductive amination, e.g. with $NaB(OAc)_3H$ or $NaBH_3CN$ (i),

followed by acylation the amino group with a carboxylic acid of formula (II):



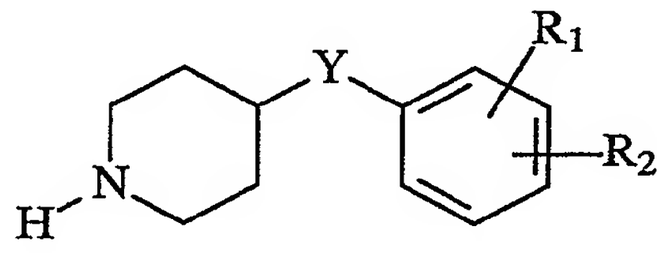
(II)

wherein Q is the same as defined above for the formula (I); or derivatives thereof (ii),

after removing the protective group (iii),

the terminal free hydroxyl group is converted into halogenide, preferably iodide or bromine, with a halogenation agent e.g. PPh_3Br_2, PPh_3I_2, preferably PPh_3I_2, (iv),

the amine derivatives of formula (IV):

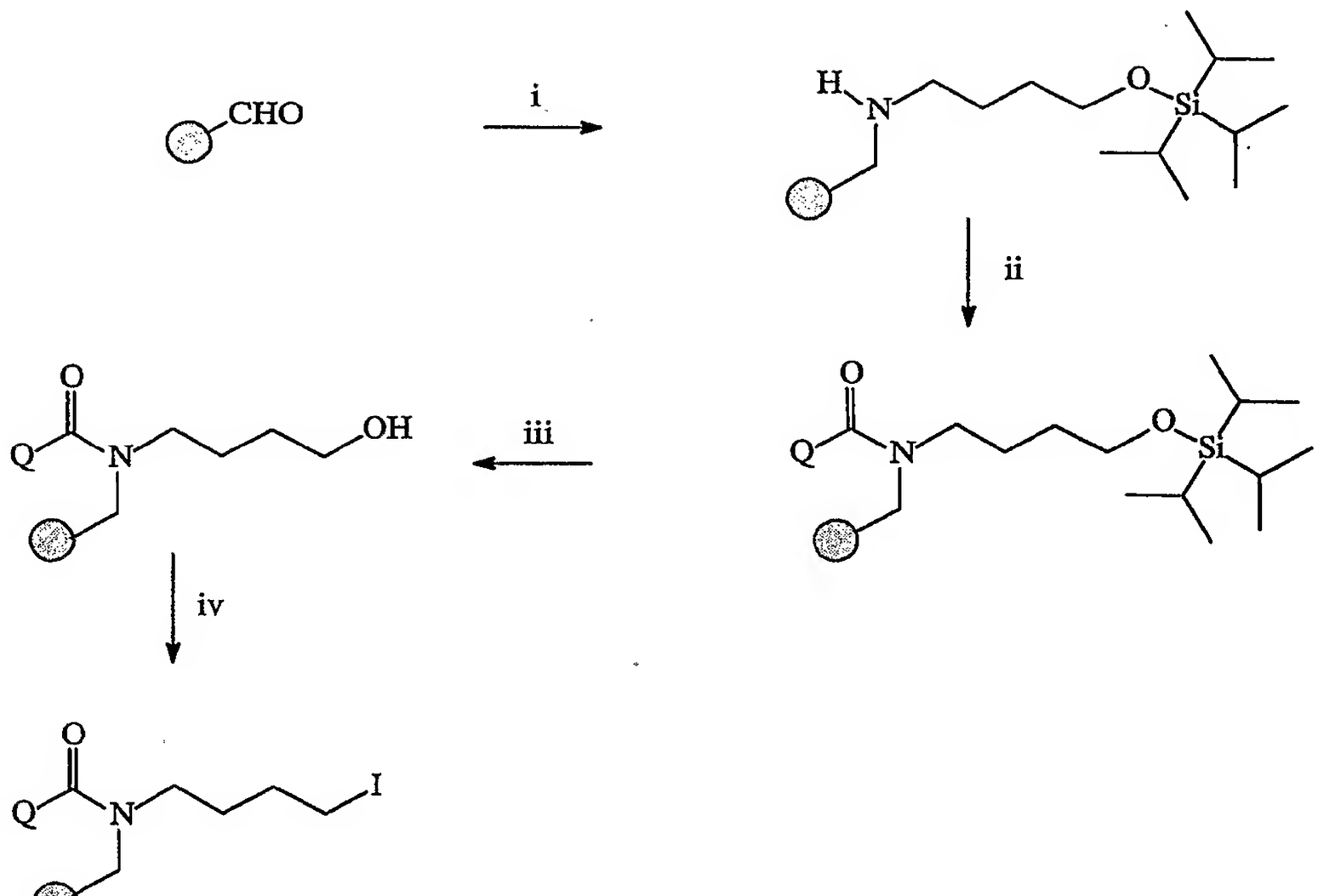


(IV)

wherein R_1, R_2 and Y are as described above for the formula (I); are alkylated with the halogenide derivative obtained in the previous step (v),

acidic cleavage released the products of formula (I) wherein R_1, R_2, Y and Q are the same meaning as defined above; from the solid-phase (vi).

This synthetic route is represented by the following Scheme.



(I)

i: "primary amine"/$NaBH(OAc)_3$/AcOH;

ii: "acid"/HBTU/TEA;

iii: Bu_4NF;

iv: I_2/Ph_3P/imidazole;

v: "secondary amine", Hünig-base;

vi: TFA/DCM.

The compounds of formula (I) of the present invention have been found to exhibit affinity for dopamine receptors, in particular the D_3 receptors, and are expected to be useful in the treatment of disease states and/or prevention the same in which dopamine D_3 receptors are involved in disease pathology and thus their modulation is required. The compounds of formula (I) have also been found to have greater afffinity for dopamine D_3 than for D_2 receptors. The compounds of formula (I) may therefore advantageously be used as selective modulators of D_3 receptors.

Dysfunction of the dopaminergic neurotransmitter system is involved in the pathology of several neuropsychiatric disorders such as schizophrenia, Parkinson's disease and drug abuse. The effect of dopamine is mediated via at least five distinct dopamine receptors belonging to the D_1- (D_1, D_5) or the D_2- (D_2, D_3, D_4) families. D_3 receptors have been shown to have characteristic distribution in the cerebral dopaminergic systems. Namely, high densities were found in certain limbic structures such as nucleus accumbens and islands of Calleja. Therefore, selective targeting of the D_3 receptors may be a promising approach for more selective modulation of dopaminergic functions and consequently for successful therapeutic intervention in several abnormalities, such as schizophrenia, emotional or cognitive dysfunctions and addiction (Sokoloff, P. et al.: Nature , **1990**, 347, 146; Schwartz, J.C. et al.: Clin. Neuropharmacol. **1993**, 16, 295; Levant, B.: Pharmacol. Rev. **1997,** 49, 231), addiction (Pilla, C. et al.: Nature **1999**, 400, 371) and Parkinson's disease (Levant, B. et al.: CNS Drugs **1999,** 12, 391) or pain (Levant, B. et al.: Neurosci. Lett. **2001**, 303, 9). Dopamine D_3 receptors are implicated in regulation of intraocular pressure and agonists at these receptor are capable of decreasing the intraocular pressure (Chu, E. et al.: J. Pharmacol. Exp. Ther. **2000**, 292, 710), thus D_3 receptors agonists can be useful for the treatment of glaucoma.The invention provides novel compounds of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof which are D_3 dopamine receptor subtype selective ligands. Certain compounds of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates

and/or solvates thereof have been found dopamine D_3 receptor antagonist, others may be full or partial agonists.

In a further aspect of the present invention provides a method of treating conditions which require modulation of dopamine D_3 receptors, for example psychoses (e.g. schizophrenia, schizo-affective disorders), psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders such as Parkinson's disease, neuroleptic induced parkinsonism, eating disorders (e.g. bulimia nervosa), depression, anxiety, memory disorders, sexual dysfunction and drug abuse, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

The invention also provides the use of a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof in the manufacture of a medicament for the treatment of conditions which require modulation of dopamine D_3 receptors.

A preferred use for D_3 antagonists according to the present invention is in the treatment of schizophrenia, schizo-affective disorders, psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders such as Parkinson's disease, neuroleptic induced parkinsonism, depression, anxiety, memory disorders, sexual dysfunction, drug abuse, pain.

A preferred use for D_3 agonists or partial agonists according to the present invention is in the treatment of drug abuse (such as cocaine abuse etc.), eye diseases (such as glaucoma).

For use in medicine, the compounds of formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a new compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and physiologically acceptable carriers.

The compounds of formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof may be administered by any convenient method, for example by oral, parental, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation of the compounds of formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof generally consists of a suspension or solution of the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof in a suitable liquid carrier(s) for example an aqueous solvent, such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the solid form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, cellulose etc.

A composition in the solid form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatine capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatine capsule.

Typical parenteral compositions consist of a solution or suspesion of the compound of formula (I) of the present invention and/or geometric isomers and/or

stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in a steril aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions of the present invention for nasal administration containing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations of the present invention typically comprise a solution or fine suspension of the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in a single or multidose quantities in steril form is a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas, such as compressed air or an organic propellant, such as a fluorochlorohydrocarbon. The aerosol dosages form can also take the form af a pump-atomiser. Compositions of the present invention containing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier, such as sugar and acacia, tragacanth, or gelatine and glycerin etc.

Compositions of the present invention containing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof for rectal

administration are conveniently in the form of suppositories containing a conventional supposiory base, such as cocoa butter.

Compositions of the present invention containing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof for transdermal administration include ointments, gels and patches.

The compositions of the present invention containing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof are preferably in the unit dose form, such as tablet, capsule or ampoule.

Each dosage unit of the present invention for oral administration contains preferably from 1 to 250mg of a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof calculated as a free base.

Each dosage unit of the present invention for parenteral administration contains preferably from 0.1 to 25mg of a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof calculated as a free base.

The physiologically acceptable compounds formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof can normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose between 1mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof calculated as the free base. The compounds of the present invention can be administered 1 to 4 times per day. The compounds of the present invention can suitably be administered for a period of continous therapy, for example for a week or more.

Biological test methods

Receptor binding assays

1. D_3 receptor binding

Binding study was carried out on rat recombinant D_3 receptors expressed in Sf9 cells using [^{3}H]-spiperone (0.4 nM) as ligand and haloperidol (10 μM) for determination of non-specific binding. The assay was performed according to Research Biochemical International assay protocol for D_3 receptor (Cat. No. D-181).

2. D_2 receptor binding

Binding of [^{3}H]-spiperone (0.5 nM) to rat striatal tissue was measured according to the method of Seeman (J. Neurochem. **1984**, 43, 221-235). The non-specific binding was determined in the presence of (±)-sulpiride (10 μM).

D_3 and D_2 receptor binding data of selected compounds of the invention are listed in the Table hereinbelow.

code	D3-IC_{50} (nM)	D2-IC_{50} (nM)
13184	2.4	516
13285	9.9	395
13662	2.8	592
13738	4.5	>3000
13758	2.3	362
13938	0.7	283
13999	1.1	201
14175	0.9	300
14201	10.3	624
14313	3.6	300

One of the most prominent side effects of the first generation antipsychotic compounds (e.g. chlorpromazine and haloperidol) with preferential blockade at dopamine D_2, and alpha-1 receptors, are the tardive dyskinesia and orthostatic hypotension. The former one is the result of blockade of D_2 receptors in the basal ganglia whereas the latter is the consequence of antagonism of alpha-1 receptors. Compounds in the above table are potent ligands at D_3 receptors (IC-50 values are between 0.7 and 10.3 nM) and show 40 to >666 fold selectivity over D_2 receptors. Moreover, the compounds have beneficial profile in terms of potency on D_3 receptors and selectivity towards D_2 receptors than the known D_3 receptor ligands which are described in the literature. It is therefore anticipated that no or greatly diminished adverse effects related to D_2 receptors will occur in the course of therapeutical application of compounds of the present invention.

The invention is further illustrated by the following non-limiting examples.

The structure of all intermediates and end products were elucidated by IR, NMR and MS spectroscopy.

Example 1

1-Phthalimidobutyl-4-(3-trifluoromethyl-phenylamino)-piperidine

A solution of 4-(3-trifluoromethyl-phenylamino)-piperidine dihydrochloride (8,0 g; 25 mmol), N-(4-bromobutyl)-phthalimide (7,1g; 25 mmol), potassium carbonate (12g; 87 mmol) and a catalytic amount of sodium iodide in acetonitrile was refluxed for 10 h. The reaction mixture was filtered. Evaporation in vacuo gave the title compound (11g; mp.:189 °C) which was used in the next step without further purification.

The following compounds were prepared in a similar manner to Example 1.

1-Phthalimidobutyl-4-(2-methoxy-phenylamino)-piperidine,
1-phthalimidobutyl-4-(2,5-dichloro-phenylamino)-piperidine,

1-phthalimidobutyl-4-(3-cyano-phenylamino)-piperidine,
1-phthalimidobutyl-4-(3,5-bis-trifluoromethyl-phenylamino)-piperidine,
1-phthalimidobutyl-4-(3,4-difluoro-phenylamino)-piperidine,
1-phthalimidobutyl-4-(3,5-difluoro-phenylamino)-piperidine,
1-phthalimidobutyl-4-(3-cyano-phenylmethyl)-piperidine,
1-phthalimidobutyl-4-(3-trifluoromethyl-phenylmethyl)-piperidine,
1-phthalimidobutyl-4-(3-cyano-phenoxy)-piperidine,
1-phthalimidobutyl-4-(3-trifluoromethyl-phenoxy)-piperidine,
1-phthalimidobutyl-4-(3-cyano-5-trifluoromethyl-phenoxy)-piperidine,
1-phthalimidobutyl-4-(3-trifluoromethyl-phenylmethoxy)-piperidine,
1-phthalimidobutyl-4-(3-hydroxy-phenylmethyl)-piperidine,

Example 2

N-[4-(3-Trifluoromethyl-phenylamino)-1-piperidinyl]-butylamine

A solution of 1-phthalimidobutyl-4-(3-trifluoromethyl-phenylamino)-piperidine (12,2g; 25 mmol) and hydrazine hydrate (1,9ml; 38 mmol) in ethanol (250ml) were stirred at room temperature for 20 h and refluxed for 1 h. The cooled reaction mixture was evaporated and acidified with 1N hydrochloric acid, filtered and the filtrate basified with 1N sodium hydroxide. The product was extracted with dichloromethane (2 x 100ml), the extracts were dried and evaporated in vacuo to afford the title compound as an oil (6,2g; 78 %), it was used in the next step without further purification.

The following compounds were prepared in a similar manner to Example 2.

N-[4-(2-methoxy-phenylamino)-1-piperidinyl]-butylamine,
N-[4-(2,5-dichloro-phenylamino)-1-piperidinyl]-butylamine,
N-[4-(3-cyano-phenylamino)-1-piperidinyl]-butylamine,
N-[4-(3,5-bis-trifluoromethyl-phenylamino)-1-piperidinyl]-butylamine,
N-[4-(3,4-difluoro-phenylamino)-1-piperidinyl]-butylamine,
N-[4-(3,5-difluoro-phenylamino)-1-piperidinyl]-butylamine,

N-[4-(3-cyano-phenylmethyl)-1-piperidinyl]-butylamine,
N-[4-(3-trifluoromethyl-phenylmethyl)-1-piperidinyl]-butylamine,
N-[4-(3-cyano-phenoxy)-1-piperidinyl]-butylamine,
N-[4-(3-trifluoromethyl-phenoxy)-1-piperidinyl]-butylamine,
N-[4-(3-cyano-5-trifluoromethyl-phenoxy)-1-piperidinyl]-butylamine,
N-[4-(3-trifluoromethyl-phenylmethoxy)-1-piperidinyl]-butylamine,
N-[4-(3-hydroxy-phenylmethyl)-1-piperidinyl]-butylamine,

Example 3

N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-4-pyridinecarboxamide (14320)

4-pyridinecarboxylic acid (0.37g; 3 mmol) was dissolved in dimethylformamide (20 ml), 1-hydroxybenztriazole (0.46g; 3 mmol) was added followed by dicyclohexylcarbodiimide (0.62g; 3 mmol), the mixture was stirred for 10 minutes at room temperature and N-[4-([3-trifluoromethyl-phenylamino)-1-piperidinyl]-butylamine (0.95g; 3 mmol) in dimethylformamide (5ml) was added and stirred at room temperature overnight. The precipitate was filtered and the solution evaporated in vacuo. The residue was partitioned between 10% $NaHCO_3$ solution and dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated in vacuo. Chromatography on silica with methanol as eluant followed by conversion to the hydrochloride salt gave the title compound (0.81 g; 51 %), melting point: 106 °C (3HCl).

The following compounds were prepared in a similar manner to Example 3.

N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-9H-β-carboline-3-carboxamide, m.p.:184 °C; (trihydrochloride mp.:208 °C) (13184)
N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-quinoline-3-carboxamide, m.p.:145-6 °C; (13775)
N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-benzimidazole-5-carboxamide, m.p.:181 °C; (13800)

4-(4-chlorobenzolsulfonylamino)-N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-benzamide dihydrochloride, m.p.:132°C ; (14313)
4-(imidazo[2,1-b]thiazol-6-yl)-N-{4-[4-(3-trifluoromethyl-phenylmethyl)-1-piperidinyl]-butyl}-benzamide dihydrochloride, m.p.:120 °C, (13759)
4-(imidazo[1,2-a]-pyrimidin-2-yl)-N-{4-[4-(3-trifluoromethyl-phenylmethyl)-1-piperidinyl]-butyl}-benzamide, m.p.: 153°C, (13890)
4'-hydroxy-4-biphenyl-N-{4-[4-(3-trifluoromethyl-phenylmethyl)-1-piperidinyl]-butyl}-carboxamide, m.p.:102 °C, (13938)
4-(pyrimidin-4-yl)-N-{4-[4-(3-trifluoromethyl-phenylmethyl)-1-piperidinyl]-butyl}-benzamide, m.p.:86 °C, (13954)
N-{4-[4-(3-trifluoromethyl-phenylmethyl)-1-piperidinyl]-butyl}-3-quinoline-carboxamide, m.p.:82 °C, (13999)
N-{4-[4-(3-trifluoromethyl-phenylmethyl)-1-piperidinyl]-butyl}-4-quinoline-carboxamide dihydrochloride, oil, (14200)
N-{4-[4-(3-cyano-phenylmethyl)-1-piperidinyl]-butyl}-4-quinolinecarboxamide, m.p.:113 °C, (70001247)
4-bromo-N-{4-[4-(3-trifluoromethyl-phenylmethyl)-1-piperidinyl]-butyl}-benzamide, m.p.:84-5 °C, (70001335)
4-(imidazo[2,1-b]thiazol-6-yl)-N-{4-[4-(3-trifluoromethyl-phenoxy)-1-piperidinyl]-butyl}-benzamide, m.p.:183-4 °C, (13758)
N-{4-[4-(3-trifluoromethyl-phenoxy)-1-piperidinyl]-butyl}-3-quinolinecarboxamide, m.p.:98 °C, (14084)
N-{4-[4-(3-trifluoromethyl-phenoxy)-1-piperidinyl]-butyl}-4-quinolinecarboxamide, m.p.:113 °C, (14201)
4-bromo-N-{4-[4-(3-trifluoromethyl-phenoxy)-1-piperidinyl]-butyl}-benzamide, m.p.:92°C, (70001334)
4-bromo-N-{4-[4-(3-cyano-5-trifluoromethyl-phenoxy)-1-piperidinyl]-butyl}-benzamide, m.p.: 121 °C; (70001768)
4-bromo-N-{4-[4-(3-cyano-phenoxy)-1-piperidinyl]-butyl}-benzamide, m.p.: 166-8°C; (70001807)

Example 4

4-Bromo-N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-benzamide (13622; 70001331)

To a solution of 4-bromo-benzoic acid (1.21g; 6 mmol) and N-methyl-morpholine (0.66ml; 6 mmol) in dimethylformamide (60ml) isobutyl chloroformate (0.93ml; 7.2 mmol) was added at –10°C, after stirring for 1hour N-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butylamine (1.5 g; 5 mmol) in dimethylformamide (15ml) was dropped in and stirred for 2 h at room temperature. The reaction mixture was evaporated in vacuo, then partitioned between chloroform (150ml) and 1N sodiumhydroxide (50ml). The organic extract was washed with water (20ml), dried and evaporated in vacuo. Conversion to the hydrochloride salt with HCl in ethylacetate gave the title compound (1.47g; 51%), melting point:141-2 °C (2 HCl).

The following compounds were prepared in a similar manner to Example 4.

5-bromo-N-{4-[4-(2-methoxy-phenylamino)-1-piperidinyl]-butyl}-pyridine-3-carboxamide trihydrochloride, m.p.:108 °C ; (13251)

4-(imidazo[2,1-b]thiazol-6-yl)-N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-benzamide, m.p.:186-8 °C; (trihidrochloride m.p.:94-100 °C (13284); (13625)

4-(imidazo[2,1-b]thiazol-6-yl)-N-{4-[4-(2-methoxy-phenylamino)-1-piperidinyl]-butyl}-benzamide, m.p.:158-9 °C; (13285)

4-(imidazo[2,1-b]thiazol-6-yl)-N-{4-[4-(2,5-dichloro-phenylamino)-1-piperidinyl]-butyl}-benzamide, m.p.:173-4 °C ; (13511)

N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-naphthalene-2-carboxamide, m.p.:117-9 °C ; (13662)

4-(imidazo[1,2-a]pyridin-2-yl)-N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-benzamide, m.p.:180-2 °C ; (13687)

4-(imidazo[1,2-a]pyrimidin-2-yl)-N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-benzamide, m.p.:224-7 °C ; (13738)

4-(imidazo[2,1-b]thiazol-6-yl)-N-{4-[4-(3-cyano-phenylamino)-1-piperidinyl]-butyl}-benzamide, m.p.:100-5 °C ; (13934)

5-methoxy-N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-benzothiophene-2-carboxamide dihydrochloride, m.p.:187 °C ; (14076)

6-methoxy-N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-benzofuran-2-carboxamide dihydrochlorid, m.p.:163-70 °C ; (14077)

N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-1H-indole-2-carboxamide, m.p.:136-41 °C ; (14078)

N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-naphthalene-1-carboxamide dihydrochloride, m.p.:201-6 °C ; (14246)

6-methoxy-N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-benzothiazole-2-carboxamide dihydrochloride, m.p.:162 °C ; (70001061)

Example 5

N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-benzamide (13565)

To a cooled solution of N-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butylamine (1.58g; 5 mmol) in chloroform (30ml) triethylamine (1.4ml) was added and benzoylchloride (0.7ml; 6 mmol) in chloroform (5ml) was dropped in at 10 °C. The temperature was allowed to rise to room temperature and stirring continued for 2 hours. 1N NaOH solution (10ml) was dropped in and stirred for half an hour. After separation the aqueous phase was extracted twice with chlorofom (20ml). The combined organic phases were washed with water, dried and evaporated in vacuo. The residue was crystallized with ether giving the title compound (0.97g; 46%), melting point: 123-5 °C.

The following compound was prepared in a similar manner to Example 5.

N-{4-[4-(3,5-bistrifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-2-methyl-butanamide dihydrochloride, m.p.:199-200 °C ; (13947)

Example 6

N-{4-[4-(3,4-difluoro-phenylamino)-1-piperidinyl]-butyl}-4-methoxybenzamide (14138)

4-methoxybenzoic acid (0.55g; 3.6 mmol) was dissolved in dimethylformamide (20ml), 1-hydroxybenztriazole (0.46g; 3 mmol) was added followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6g; 3.6 mmol), the mixture was stirred for 10 minutes at room temperature and N-[4-([3,4-difluoro-phenylamino)-1-piperidinyl]-butylamine (1.02g; 3.6 mmol) in dimethylformamide (5ml) was added and stirred overnight at room temperature. The precipitate was filtered and the solution evaporated in vacuo. The residue was partitioned between 10% $NaHCO_3$ solution and dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated in vacuo. Chromatography on silica with dichloromethane:methanol 15:1 as eluant followed by crystallization from diisopropylether gave the title compound (0.48g; 28%), melting at 106-7 °C.

The following compounds were prepared in a similar manner to Example 6.

N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-1H-indole-5-carboxamide dihydrochloride, .m.p.: 204 °C ; (14175)

N-{4-[4-(2,5-difluoro-phenylamino)-1-piperidinyl]-butyl}-4-methoxy-benzamide, oil; (14239)

N-{4-[4-(3-trifluoromethyl-phenylamino)-1-piperidinyl]-butyl}-3-(1H-indol-3-yl)-2-propenamide, oil; (70001204)

N-{4-[4-(3-trifluoromethyl-phenylmethoxy)-1-piperidinyl]-butyl}-4-quinoline-carboxamide hydrochloride, m.p.:57°C; (70001809)

4-bromo-N-{4-[4-(3-hydroxy-phenylmethyl)-1-piperidinyl]-butyl}-benzamide, m.p.: 98°C; (70001970)

N-{4-[4-(3-trifluoromethyl-phenylmethyl)-1-piperidinyl]-butyl}-3-pyridineacrylamide dihydrochloride, m.p.: 109°C; (70002025)

Example 7

5-Bromo-N-{4-[4-(2-hydroxy-phenylamino)-1-piperidinyl]-butyl}-pyridine-3-carboxamide (13330)

To a solution of 5-bromo-N-{4-[4-(2-methoxy-phenylamino)-1-piperidinyl]-butyl}-pyridine-3-carboxamide, (3.4g; 7.4 mmol) in dichloromethane (50ml) 1.0M boron tribromide solution in dichloromethane (14.8ml) was added and stirred for 6 h at room temperature. The reaction mixture was poured into 8% $NaHCO_3$ solution (100ml), separated and the aqueous phase extracted twice with dichloromethane. The organic phases were dried and evaporated in vacuo. The residue was purified by chromathograpy on silica (chloroform/methanol 3/1, then 1/1) to give the title compound (0.6g; 18%), melting point: 55-58 °C.

The following compound was prepared in a similar manner to Example 7.

4-(imidazo[2,1-b]thiazol-6-yl)-N-{4-[4-(2-hydroxy-phenylamino)-1-piperidinyl]-butyl}-benzamide, m.p.:195-200 °C . (13567)

Example 8

5-Bromo-N-{4-[4-(2-methanesulfonyloxy-phenylamino)-1-piperidinyl]-butyl}-pyridine-3-carboxamide (13509)

To a solution of 5-bromo-N-{4-[4-(2-hydroxy-phenylamino)-1-piperidinyl]-butyl}-pyridine-3-carboxamide (0.9g; 2 mmol) in dichloromethane triethylamine (2ml) was added and cooled to + 5 °C, methanesulfonylchloride (0.23ml; 3 mmol) in dichloromethane (10ml) was dropped in and the mixture stirred overnight at room temperature. The solution was washed twice with water (30ml), dried and evaporated in vacuo. Conversion to the trihydrochloric acid salt gave the title compound (0,36g; 28.4%), melting point: 115-20 °C.

The following compound was prepared in a similar manner to Example 8.

4-(imidazo[2,1-b]thiazol-6-yl)-N-{4-[4-(2-methanesulfonyloxy-phenylamino)-1-piperidinyl]-butyl}-benzamide, oil. (13663)

Example 9

4-bromo-N-{4-[4-(3-aminocarbonyl-phenoxy)-1-piperidinyl]-butyl}-benzamide (70002160)

0.32g (0.7 mmol) of 4-bromo-N-{4-[4-(3-cyano-phenoxy)-1-piperidinyl]-butyl}-benzamide was dissolved in 2ml dimethylsulfoxide, 80mg K_2CO_3 was added and 0.15ml of 30% H_2O_2 was dropped in while keeping the temperature at 20 ^{0}C. After stirring for 2 h 20 ml of water was added, the precipitate filtered, washed with water giving the title compound (0.22g; 66%), melting point:149°C.

Example 10

Triisopropylsilanyloxy-butylamine

10g (0.11 mol) of 4-aminobutanol and 16.5ml (0.12 mol) of triethylamine was dissolved in 100ml dichloromethane. To the ice-cooled solution 24ml (0.12 mol) chlorotriisopropylsilane was added in 50ml dichloromethane. The mixture was stirred for 20 hours at room temperature. The resulted suspension was extracted with 300ml of water. The water phase was further extracted with 3 x 50 ml dichloromethane. The combined organic solutions were dried and evaporated in vacuum to give 26.5g (96%) of triisopropylsilanyloxy-butylamine.

Example 11

Polymer bound triisopropylsilanyloxy-butylamine

10g (16 mmol) 4-formyl-3-methoxy-phenoxy polystyrene was suspended in 400ml dichloromethane. 17.2g (70 mmol) triisopropylsilanyloxy-butylamine was added dropwise to the slowly stirred resin suspension within 5 minutes, followed by 12.6ml glacial acetic acid. 15g (70 mmol) sodium triacetoxyborohydride was also added in small portion within 30 minutes. After 3 hours another 6g (28.5

mmol) sodium triacetoxyborohydride was added to the suspension. The stirring was continued for 16 hours. The resin was filtered, and washed twice with 400ml of the following solvents in sequence: methylene chloride, methanol, 10% triethylamine in dimethylformamide, methanol, dimethylformamide, tetrahydrofurane. The resin was dried in vacuum. The resulted resin had a weight of 12.9g

Example 12

Polymer-bound N-(4-triisopropylsilanyloxy-butyl)-benzamide

To 0.12g (0.14 mmol) of polymer-bound 4-triisopropylsilanyloxy-butylamin 1.26ml (0.63 mmol) of 0.5M benzoic acid in dimethylformamide was added. It was shaken on an orbital shaker with 100 1/min rotations for 5 min, then 0.24ml (0.42 mmol) of 25% triethylamine in dimethylformamide and 1.26ml (0.63 mmol) of 0.5 M HBTU in dimethylformamide were added. The reaction mixture was shaken on an orbital shaker with 100 1/min rotations at room temperature for 5 h. Then the resin was filtered and washed twice with 4 ml of dimethylformamide, twice with 4ml of methanol, twice with 4ml of THF, twice with 4ml of methanol and twice with 4ml of THF.

Example 13

Polymer-bound N-(4-hydroxybutyl)-benzamide

To polymer-bound N-(4-triisopropylsilanyloxy-butyl)-benzamide obtained in the previous step 0.11g (0.42 mmol) of tetrabutylammonium fluoride hydrate in 2ml of tetrahydrofuran was added. The reaction mixture was shaken on an orbital shaker with 100 1/min rotations at room temperature for 1 h, the resin was filtered and 0.11g (0.42 mmol) of tetrabutylammonium fluoride hydrate in 2ml of tetrahydrofuran was added again. The reaction mixture was shaken on an orbital shaker with 100 1/min rotations at room temperature for 1 h. Then the resin was

filtered and washed twice with 4ml of THF, twice with 4ml of methanol, twice with 4ml of dichloromethane, twice with 4ml of methanol, twice with 4ml of THF, twice with 4ml of methanol and finally twice with 4ml of dichloromethane.

Example 14

Polymer-bound N-(4-iodobutyl)-benzamide

To polymer-bound N-(4-hydroxybutyl)-benzamide obtained in the previous step 0.037 g (0.56 mmol) of imidazole in 0.56ml of dichloromethane was added. After 5 min shaking 0.289g (0.56 mmol) of diiodotriphenylphosphorane in 3.73ml of dichloromethane was added. The reaction mixture was shaken on an orbital shaker with 100 1/min rotations at room temperature for 7 h. Then the resin was filtered and washed three times with 4 ml of dichloromethane, twice with 4ml of methanol, twice with 4ml of dichloromethane, three times with 6ml of dimethylformamide.

Example 15

Polymer-bound N-{4-[4-(3-methoxy-phenylamino)-piperidin-1-yl]-butyl}-benzamide

To polymer-bound N-(4-iodobutyl)-benzamide obtained in the previous step 0.102g (0.48 mmol) of 1-(3-methoxyphenylamino)-piperidine in 0.48ml of dimethylformamide was added. It was shaken on an orbital shaker with 100 1/min rotations for 5 min, then 0.29ml (0.48 mmol) of 25% diisopropylethylamine in dimethylformamide is added. The reaction mixture was shaken on an orbital shaker with 100 1/min rotations at 95 ^{0}C for 3 h. Then the resin was filtered and washed twice with 4ml of dimethylformamide twice with 4ml of methanol, twice with 4 ml of dichloromethane, twice with 4ml of dimethylformamide and three times with 2ml of dichloromethane.

Example 16

N-{4-[4-(3-Methoxy-phenylamino)-piperidin-1-yl]-butyl}-benzamide

A mixture of polymer-bound N-{4-[4-(3-methoxy-phenylamino)-piperidin-1-yl]-butyl}-benzamide obtained in the previous step and 2ml of a 1 : 2 mixture of trifluoroacetic acid : dichloromethane was shaken on an orbital shaker with 100 1/min rotations for 2 h. Then the resin was filtered off and washed twice with 2ml of dichloromethane. The combined filtrate is concentrated in vacuo to yield the title compound.

The LC/MS analysis were performed using an HP 1100 binary gradient system, controlled by ChemStation software. HP diode array detector was used to acquire UV spectra at λ = 240 nm. Analytical chromatographic experiments were made on Discovery C_{16}-Amide, 5 cm X 4.6 mm X 5 µm column with a flow rate of 1 ml/min for qualification (purity, capacity factor). All experiments were performed using HP MSD single quadruple mass spectrometer equipped with an electrospray ionisation source to determine the structure.

k'= capacity factor

$k' = t_R - t_0 / t_0$

t_R = retention time

t_0 = eluent retention time

The following compounds were prepared in a similar manner to Example 16.

ID	Name	fmla structure	MW	MS found MW	k'
80000001	{4-[4-(3-Methoxy-phenylamino)-piperidin-1-yl]-butyl}-benzamide	C23H31N3O2	381,5	382,2	2,597
80000034	{4-[4-(4-Chloro-naphthalen-1-ylamino)-piperidin-1-yl]-butyl}-4-sulfamoyl-benzamide	C26H31ClN4O3S	515,1	516,9	4,094
80000056	{4-[4-(2,6-Dimethyl-phenylamino)-piperidin-1-yl]-butyl}-2,4-difluoro-benzamide	C24H31F2N3O	415,5	416,3	2,576
80000112	{4-[4-(2,5-Dichloro-phenylamino)-piperidin-1-yl]-butyl}-3,4,5-triethoxy-benzamide	C28H39Cl2N3O4	552,5	554,3	4,116
80000684	4-Methoxy-quinoline-2-carboxylic acid {4-[4-(4-bromo-phenylamino)-piperidin-1-yl]-butyl}-amide	C26H31BrN4O2	511,4	512,4	3,229

Example 17

4-(Imidazo[2,1-b]thiazol)-6-yl)-benzoic acid

22.4g (0.1 mol) of 4-(2'-bromo-acetyl)-benzonitrile was added to a solution of 10g (0.1 mol) of 2-amino-thiazole in 100ml of acetone, and the mixture was refluxed for 1 hour. The obtained suspension was cooled and stored at 5°C for 16 hours. The intermediate quaternary compound was filtered off, and washed with 20ml of diisipropyl-ether. The solid was suspended in 600ml of 5N aqueous hydrochloric acid, and was heated under reflux for 60 hours. The solvent was evaporated in vacuo and the residue was dissolved in 200ml of 2.5N aqueous sodium hydroxide. The solution was decolorized with 5g of carbon and the pH was adjusted to 4.5 with 5N aqueous hydrochloric acid.The suspension was cooled to 10°C and filtered. The solid was washed with ice water (2 x 50 ml) and dried in vacuo at 140°C overnight to give the title compound,16.7g (72%) melting at 312-315°C.

The following compound was prepared in a similar manner to Example 17.

4-(imidazo[1,2-a]pyrimidin-2-yl)-benzoic acid, m.p.: above 320°C (starting from 2-amino-pyrimidine).

Example 18

Pharmaceutical formulation

a) Intravenous injection

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Solvent/complexing agent	to 100 ml

b) Bolus injenction

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7

Co-solvent	to 5 ml

Buffer: suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.

Solvent: typically water but may also include cyclodextrins (1-100 mg) and co-solvents, such as propylene glycol, polyethylene glycol and alcohol.

c) Tablet

Compound of formula (I)	1-40 mg
Diluent/Filter(may also include cyclodextrins)	50-250 mg
Binder	5-25 mg
Disintegrant (may also include cyclodextrins)	5-50 mg
Lubricant	1-5 mg
Cyclodextrin	1-100 mg

Diluent: e.g. mycrocrystalline cellulose, lactose starch.

Binder: e.g. polyvinylpyrrolidone, hydroxypropylmethylcellulose.

Disintegrant: e.g. sodium starch glycolate, crospovidone.

Lubricant: e.g. magnesium stearate, sodium stearyl fumarate

d) Oral suspension

Compound of formula (I)	1-40 mg
Suspending agent	0.1-10 mg
Diluent	20-60 mg
Preservative	0.01-1.0 mg
Buffer	to pH ca 5-8
Co-solvent	0-40 mg
Flavour	0.01-1.0 mg
Colourant	0.001-0.1 mg

Suspending agent:e.g. xanthan gum, mycrocrystalline

cellulose.

Diluent: e.g. sorbitol solution, tipically water.

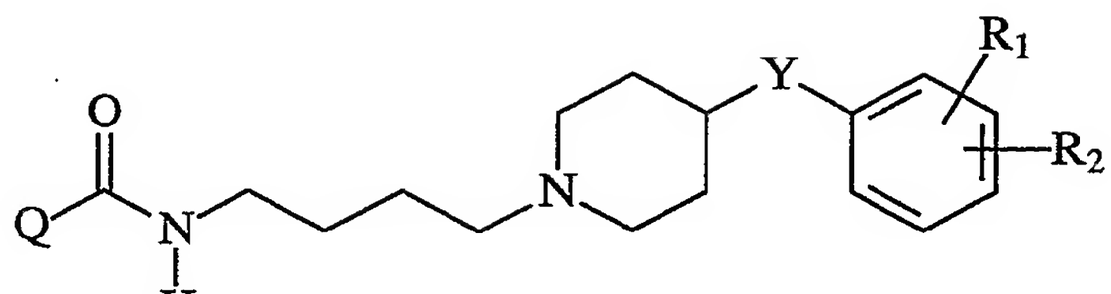
Preservative: e.g. sodium benzoate.

Buffer: e.g. citrate.

Co-solvent: e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin.

What we claim:

1. A compound of formula (I):



(I)

wherein

R_1 and R_2 represent independently a substituent selected from hydrogen, halogen, C_{1-6}alkyl, C_{1-6} alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6} alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6} alkanoyloxy, amino, aminoalkyl, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl or mono or bicyclic heterocyclic group;

Y represents an oxygen atom or NH or CH_2 or OCH_2 group;

Q represents an optionally substituted C_{1-6}alkyl, aryl, heteroaryl, heteroaralkyl or heteroaralkenyl group;

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

2. A compound as claimed in claim 1,

wherein

R_1 and R_2 represent independently halogen, trifluoromethyl, cyano, alkoxy, alkyl, hydroxy, alkansulfonyloxy, or aminocarbonyl;

Q represents optionally substituted alkyl, phenyl, biphenylyl, naphthyl, pyridyl, indolyl, indolylethenyl, carbolinyl, benzothiophen-yl, benzofuranyl or quinolinyl;

Y represents an oxygen atom or NH or CH_2 or OCH_2 group;

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

3. A compound as claimed in claim 1,

wherein

R_1 and R_2 represent independently halogen or trifluoromethyl;

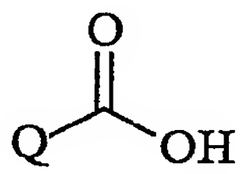
Q represents 4-methylphenyl, 4-bromophenyl, 4-chlorophenyl, 2-naphthyl, 4'-hydroxy-biphenylyl, indol-5-yl, indol-3-ethenyl, 4-(imidazo[2,1-b]thiazol-6-yl)phenyl, 4-(imidazo[1,2-a]pyridin-2-yl)phenyl, β-carbolin-3-yl, 5-methoxy-benzothiophene-2-yl, 6-methoxy-benzofuran-2-yl, 3-quinolinyl, 4-quinolinyl;

Y represents an oxygen atom or NH or CH_2 group;

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

4. A process for preparing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof as defined in any of claims 1 to 3 which comprises:

reacting a compound of formula (II):



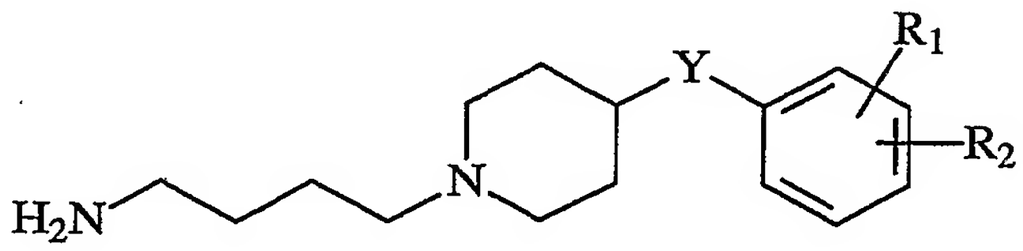
(II)

wherein

Q is as defined in any of claims 1 to 3;

or derivatives thereof

with a compound of formula (III):



(III)

wherein R_1, R_2 and Y are as defined in any of claims 1 to 3;

or derivatives thereof;

interconverting one compound of formula (I) wherein Q, R_1, R_2 and Y are as hereinbefore defined, to a different compound of formula (I) wherein Q, R_1, R_2 and Y are as defined in any of claims 1 to 3;

where appropriate, separating the enantiomers and/or diastereomers, and/or *cis*- and/or *trans*- isomers of compounds of formula (I), or intermediates thereto wherein Q, R_1, R_2 and Y are as defined in any of claims 1 to 3 by conventional methods;

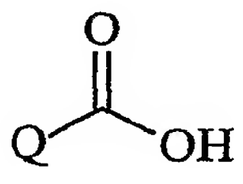
and optionally thereafter forming salts and/or hydrates and/or solvates as defined in any of claims 1 to 3.

5. A process for preparing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof as defined in any of claims 1 to 3 which comprises:preparing a compound of formula (I) on solid support.

6. A process according to claim 5 which comprises:

(i) attaching a protected 4-amino-butanol derivative to a polystyrene resin by reductive amination;

(ii) acylating the amino group of the compounds obtained with carboxylic acid of formula (II):



(II)

wherein

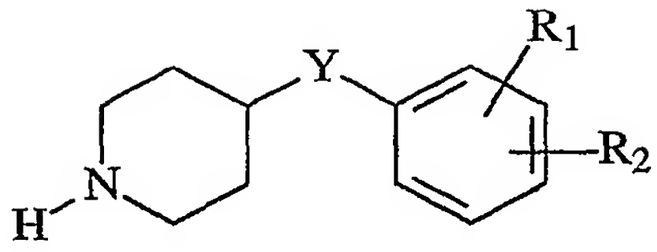
Q is as defined in claim 5;

or derivatives thereof;

(iii) removing the O-protective group from the compound obtained;

(iv) converting the terminal free hydroxyl group into halogenide with a halogenation agent;

(v) alkylating the amine derivatives of formula (IV):



(IV)

wherein R_1, R_2 and Y are as defined in claim 5;

with the halogenide derivative obtained in the previous step;

(vi) releasing compounds of formula (I) wherein R_1, R_2 and Y are as defined in claim 5; from the solid support by cleavage; and if desired

interconverting one compound of formula (I) wherein Q, R_1, R_2 and Y are as defined in claim 5 to a different compound of formula (I) wherein Q, R_1, R_2 and Y are as defined in claim 5;

where appropriate, separating the enantiomers and/or diastereomers, and/or *cis*- and/or *trans*- isomers of compounds of formula (I), or intermediates thereto, wherein Q, R_1, R_2 and Y are as defined in claim 5; by conventional methods;

and optionally thereafter forming a salt and/or hydrate and/or solvate of formula (I) wherein Q, R_1, R_2 and Y are as defined in claim 5.

7. A pharmaceutical composition comprising a compound of formula (I) as claimed in any of claims 1 to 3 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and physiologically acceptable carrier(s) therefore.

8. The use of a compound of formula (I) as claimed in any of claims 1 to 3 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in the manufacture of a medicament for the treatment and/or prevention of a condition which requires modulation of dopamine receptor(s).

9. The use according to claim 8 wherein the dopamine receptor is a dopamine D_3 receptor.

10. A method of treating and/or preventing a condition which requires modulation of dopamine receptor(s) which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as claimed in any of claims 1 to 3 and/or geometric isomers and/ or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof.

11. The method according to claim 10 wherein the dopamine receptor is a dopamine D_3 receptor.

INTERNATIONAL SEARCH REPORT

Int[illegible]onal Application No
PCT/HU 02/00094

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4468 A61K31/4523 A61K31/4535 A61K31/4545 A61K31/519
A61K31/4709 C07D211/58 C07D211/26 C07D211/46 C07D401/12
C07D471/04 C07D513/04 C07D487/04 C07D409/12 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 02 055496 A (BOMBRUN AGNES ;BOUILLOT ANNE MARIE JEANNE (FR); DUMAITRE BERNARD A) 18 July 2002 (2002-07-18) examples 19,38 claim 1 ---	1,2,7
X	US 6 235 731 B1 (SHIBOUTA YUMIKO ET AL) 22 May 2001 (2001-05-22) cited in the application example 28 claim 1 ---	1,7
X	US 5 767 131 A (CHIU GEORGE ET AL) 16 June 1998 (1998-06-16) cited in the application column 3, line 32 -column 4, line 17 ---	1,2,7
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 2002	27/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fanni, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/HU 02/00094

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 A61K31/445 C07D211/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 34889 A (CHEN XI ;NEUROGEN CORP (US); YUAN JUN (US)) 25 September 1997 (1997-09-25) page 3, line 2 - line 28 claim 1 ---	1,7-11
Y	WO 99 21848 A (HE XIAO SHU ;NEUROGEN CORP (US); COSTA BRIAN DE (US); WASLEY JAN W) 6 May 1999 (1999-05-06) page 4, paragraph 1 - paragraph 2 ---	1,7-11
Y	WO 99 02503 A (LE BRIS THEOPHILE MARIE ;NEUMANN SCHULTZ BARBARA (DE); BASF AG (DE) 21 January 1999 (1999-01-21) page 1, paragraph 1 tables 1-3,5 claim 1 -----	1,7-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fanni, S

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 11 and 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 10-11

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

national application No.
PCT/HU 02/00094

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10-11
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 02/00094

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DE 69705035 T2	14-02-2002
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